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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/039,317 | 10/23/2001 | E. Scott Priestley | PH-7148 | 8295 |

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| EXAMINER | |
|---|---|
| AUDET, MAURY A | |
| **ART UNIT** | **PAPER NUMBER** |
| 1654 | |

DATE MAILED: 11/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/039,317 | PRIESTLEY | |
| | Examin r | Art Unit | |
| | Maury Audet | 1654 | |

*-- Th MAILING DATE of this communication appears on the cover sh t with the c rrespondenc address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disp sition of Claims**

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Election/Restrictions*

In the restriction requirement of October 3, 2003, Applicant was required to elect Group I (compound/composition) or Group II (methods of using the composition), **as well as elect, as drawn to the elected group, a single compound as the invention** (not to be confused with species, as clearly laid out **in bold** in the restriction requirement page 3).

Applicant's election with traverse of Group I, claims 1-13, and the compound 2-pyrazinecarbonyl)-Val-Val-Hyp (Obzl)-(1R)-1-amino-3(4-trifluoromethyl) phenylpropylboronic acid (+)-pinanediol ester (found in the last compound of claim 12 and also in Example 34, page 118 of specification)), in the response filed October 24, 2003 is acknowledged. Note, as discussed further above, that the election of the above compound is an election of the invention, not a species. The traversal is on the ground(s) that it would not be an undue search burden on the examiner to search for both the elected compound and methods of using the compound because "any search for one set of claims is, or is nearly, coextensive with the other". This is not found persuasive because a search of a specific compound is a database structure search only; whereas the search for methods of using a compounds is generally a text-based search, which involves searching for the compound or related compounds used in similar methods. Therefore, the searches are not "coextensive" and applicant has not satisfied the burden of showing that a search of both groups would not be an undue burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

However, in this case, claims 1-12, as drawn to elected **invention** compound (2-pyrazinecarbonyl)-Val-Val-Hyp (Obzl)-(1R)-1-amino-3(4-trifluoromethyl) phenylpropylboronic

acid (+)-pinanediol ester; have been found to be directed to an allowable product (elected compound). Pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), claims 13-15, directed to the process of making or using the patentable product [among other distinct compounds], previously withdrawn from consideration as a result of a restriction requirement, are now subject to being rejoined. Claims 13-15 are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Since all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, the restriction requirement of October 3, 2003 is hereby withdrawn.

***Claim Rejections - 35 USC § 112 1st***

Claims 13-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for a "pharmaceutical" composition comprising the elected compound 2-pyrazinecarbonyl)-Val-Val-Hyp (Obzl)-(1R)-1-amino-3(4-trifluoromethyl) phenylpropylboronic acid (+)-pinanediol ester, or for methods of use, in the treatment of a viral infection and more specifically for the treatment of hepatitis C virus (HCV) infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention.

> The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the

> courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for a "pharmaceutical" composition and for methods of treating viral infection by administering the claimed compound, for the following reasons:

*The nature of the invention:* The claimed invention is generally drawn to a pharmaceutical composition (claim 13), comprising the elected compound 2-pyrazinecarbonyl)-Val-Val-Hyp (Obzl)-(1R)-1-amino-3(4-trifluoromethyl) phenylpropylboronic acid (+)-pinanediol ester, and for methods of treating viral infection and more specifically HCV infection by administration of the compound.

*The state of the prior art and the predictability or lack thereof in the art:*

> The art teaches that "NS3 is part of a large polyprotein and associates with other virally encoded protein domains; thus, it is important to characterize these functional sites, which could constitute targets for protein-protein interaction inhibitors. *The NS3 minibody ligands may well be useful molecules for interfering with viral assembly,* as they could inhibit interactions between NS3 and other uncharacterized viral or host factors. *Unfortunately, the lack of a biological assay currently hampers these experiments*" (See Dimasi et al., J Virol. 1997 Oct;71(10):7461-9, specifically "Discussion" page 7468, last ¶; emphasis added).
>
> The art further teaches that the efficacy of therapeutics is dependent upon factors such as solubility of the drug, bioavailability at the target site, attainment of effective plasma concentrations, solubility in tissues, biotransformation, toxicity, proteolytic degradation, immunological inactivation, rate of excretion or clearance (half-life), deactivation by the liver, hydrolysis in serum, binding to plasma protein, and in the case of antivirals,

propensity for emergence of resistant strains (see Benet et al., pp. 3-32, in The Pharmacological Basis of Therapeutics, 8th ed., 1990, page 3, first paragraph; page 5, second column, last partial paragraph, first two sentences; page 10, the paragraph bridging columns 1 and 2; page 18, the paragraph bridging columns 1 and 2; page 20, last full paragraph; and the paragraph bridging pages 20 and 21 and footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO BD> APP>& Inter. 1992).

Isolation, purification, formulation, and delivery of proteins represent significant challenges to pharmaceutical scientists, as proteins possess unique chemical and physical properties. These properties pose difficult stability problems (Abstract). With the recent advances in recombinant DNA technology, the commercial production of proteins for pharmaceutical purposes has become feasible. [] Unfortunately, proteins possess chemical and physical properties which present unique difficulties in the purification, separation, storage, and delivery of these materials. (Manning et al., Pharmaceutical Research, p. 903).

*The amount of direction or guidance present and the presence or absence of working examples:* Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The specification describes in the "Summary of the Invention" that the elected peptide compound may be useful [i.e. in a pharmaceutical composition] as "an inhibitor of hepatitis C virus protease, more specifically, the (hepatitis C virus) NS3 protease". The specification describes that the compounds "are **expected** to inhibit the activity of hepatitis C virus protease" (page 126, emphasis added). Further, the only testing was to the effectiveness of an enzyme assay (page 129, line 30). Additionally, the description of testing the composition/elected compound in a "cell assay" (i.e. referred to above by Dimasi et al. as a "biological assay") is only prophetic, and has not actually conducted (page 129-130). Although applicant did *design* a cell assay to overcome this difficulty (HCV will not replicate to lytic infection in cell cultures) (page 129-130); there was no data generated from actual experiments. Therefore, it is unclear how the composition/elected compound could be administered to a cell either in vitro or in vivo, so as to effectively target/inhibit HCV NS3

protease, or a protease of any other virus. Thus, the specification does not describe that the elected compound was actually found to be useful (i.e. tested) in a "pharmaceutical" composition for treating a subject with HCV or any other virus/infection.

*The breadth of the claims and the quantity of experimentation needed:* The claims are drawn broadly to a "pharmaceutical" composition and for methods of treating viral infection by administering the claimed compound. Absent sufficient teachings in the specification or art sufficient to overcome the teachings of unpredictability in the art as to enablement on whether the elected peptide can be "therapeutically effective" as a "pharmaceutical" composition (for any virus/infection, including HCV); it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maury Audet whose telephone number is 703-305-5039. The examiner can normally be reached from 7:00 AM – 5:30 PM, off Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at 703-306-3220. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-1234 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

MA
November 25, 2003

Brenda Brumback
BRENDA BRUMBACK
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TECHNOLOGY CENTER 1600